FORM LG-4878

Contains No CBI 8EHQ-0992-1313

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DU PONT

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E. I. DU PONT DE NEMOURS & COMPANY
INCORPORATED

WILMINGTON, DELAWARE 19898

LEGAL DEPARTMENT

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September 11, 1992

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Office of Pollution Prevention and Toxics
Environmental Protection Agency
401 M Street., S.W.
Washington, D.C. 20460
Attn: Section 8(e) Coordinator (CAP Agreement)

8EHQ-92-13136
INIT 09/22/92

Dear Coordinator:

8ECAP-0025

On behalf of the Regulatee and pursuant to Unit II B.1.b. and Unit II C of the 6/28/91CAP Agreement, E.I. Du Pont de Nemours and Co. hereby submits (*in triplicate*) the attached studies. Submission of this information is voluntary and is occasioned by unilateral changes in EPA's standard as to what EPA now considers as reportable information. Regulatee's submission of information is made solely in response to the new EPA §8(e) reporting standards and is not an admission: (1) of TSCA violation or liability; (2) that Regulatee's activities with the study compounds reasonably support a conclusion of substantial health or environmental risk or (3) that the studies themselves reasonably support a conclusion of substantial health or environmental risk.

The "Reporting Guide" creates new TSCA 8(e) reporting criteria which were not previously announced by EPA in its 1978 Statement of Interpretation and Enforcement Policy, 43 Fed Reg 11110 (March 16, 1978). The "Reporting Guide states criteria which expands upon and conflicts with the 1978 Statement of Interpretation. Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" raises significant due processes issues and clouds the appropriate reporting standard by which regulated persons can assure TSCA Section 8(e) compliance.

For Regulatee,

OLE CAP

88920010939

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mm
3/23/95

ATTACHMENT 1

Submission of information is made under the 6/28/91 CAP Agreement, Unit II. This submission is made voluntarily and is occasioned by recent changes in EPA's TSCA §8(e) reporting standard; such changes made, for the first time in 1991 and 1992 without prior notice and in violation of Regulatee's constitutional due process rights. Regulatee's submission of information under this changed standard is not a waiver of its due process rights; an admission of TSCA violation or liability, or an admission that Regulatee's activities with the study compounds reasonably support a conclusion of substantial risk to health or to the environment. Regulatee has historically relied in good faith upon the 1978 Statement of Interpretation and Enforcement Policy criteria for determining whether study information is reportable under TSCA §8(e), 43 Fed Reg 11110 (March 16, 1978). EPA has not, to date, amended this Statement of Interpretation.

After CAP registration, EPA provided the Regulatee the June 1, 1991 "TSCA Section 8(e) Reporting Guide". This "Guide" has been further amended by EPA, EPA letter, April 10, 1992. EPA has not indicated that the "Reporting Guide" or the April 1992 amendment supersedes the 1978 Statement of Interpretation. The "Reporting Guide" and April 1992 amendment substantively lowers the Statement of Interpretation 's TSCA §8(e) reporting standard[2]. This is particularly troublesome as the "Reporting Guide" states criteria, applied retroactively, which expands upon and conflicts with the Statement of Interpretation.[3] Absent amendment of the Statement of Interpretation, the informal issuance of the "Reporting Guide" and the April 1992 amendment clouds the appropriate standard by which regulated persons must assess information for purposes of TSCA §8(e).

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[2]In sharp contrast to the Agency's 1977 and 1978 actions to soliciting public comment on the proposed and final §8(e) Policy, EPA has unilaterally pronounced §8(e) substantive reporting criteria in the 1991 Section 8(e) Guide without public notice and comment, See 42 Fed Reg 45362 (9/9/77), "Notification of Substantial Risk under Section 8(e): Proposed Guidance".

[3]A comparison of the 1978 Statement of Interpretation and the 1992 "Reporting Guide" is a appended.

Throughout the CAP, EPA has mischaracterized the 1991 guidance as reflecting "longstanding" EPA policy concerning the standards by which toxicity information should be reviewed for purposes of §8(e) compliance. Regulatee recognizes that experience with the 1978 Statement of Interpretation may cause a review of its criteri. Regulatee supports and has no objection to the Agency's amending reporting criteria *provided that* such amendment is not applied to the regulated community in an unfair way. However, with the unilateral announcement of the CAP under the auspices of an OCM enforcement proceeding, EPA has wrought a terrific unfairness since much of the criteria EPA has espoused in the June 1991 Reporting Guide and in the Agency's April 2, 1992 amendment is new criteria which does not exist in the 1978 Statement of Interpretation and Enforcement Policy.

The following examples of new criteria contained in the "Reporting Guide" that is not contained in the Statement of Interpretation follow:

- o even though EPA expressly disclaims each "status report" as being preliminary evaluations that should not be regarded as final EPA policy or intent[4], the "Reporting Guide" gives the "status reports" great weight as "sound and adequate basis" from which to determine mandatory reporting obligations. ("Guide" at page 20).
- o the "Reporting Guide" contains a matrix that establishes new numerical reporting "cutoff" concentrations for acute lethality information ("Guide" at p. 31). Neither this matrix nor the cutoff values therein are contained in the Statement of Interpretation. The regulated community was not made aware of these cutoff values prior to issuance of the "Reporting Guide" in June, 1991.
- othe "Reporting Guide" states new specific definitional criteria with which the Agency, for the first time, defines as 'distinguishable neurotoxicological effects'; such criteria/guidance not expressed in the 1978 Statement of Interpretation.[5];

- othe "Reporting Guide" provides new review/ reporting criteria for irritation and sensitization studies; such criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy.
- othe "Reporting Guide" publicizes certain EPA Q/A criteria issued to the Monsanto Co. in 1989 which are not in the Statement of Interpretation; have never been published in the Federal Register or distributed by the EPA to the Regulatee. Such Q/A establishes new reporting criteria not previously found in the 1978 Statement of Interpretation/Enforcement Policy .

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[4]The 'status reports' address the significance, if any, of particular information reported to the Agency, rather than stating EPA's interpretation of §8(e) reporting criteria. In the infrequent instances in which the status reports contain discussion of reportability, the analysis is invariably quite limited, without substantial supporting scientific or legal rationale.

[5] *See, e.g,* 10/2/91 letter from Du Pont to EPA regarding the definition of 'serious and prolonged effects' as this term may relate to transient anesthetic effects observed at lethal levels; 10/1/91 letter from the American Petroleum Institute to EPA regarding clarification of the Reporting Guide criteria.

In discharging its responsibilities, an administrative agency must give the regulated community fair and adequate warning to as what constitutes noncompliance for which penalties may be assessed.

> Among the myriad applications of the due process clause is the fundamental principle that statutes and regulations which purport to govern conduct must give an adequate warning of what they command or forbid.... Even a regulation which governs purely economic or commercial activities, if its violation can engender penalties, must be so framed as to provide a constitutionally adequate warning to those whose activities are governed.

Diebold, Inc. v. Marshall, 585 F.2d 1327, 1335-36 (D.C. Cir. 1978). *See also*, Rollins Environemntal Services (NJ) Inc. v. U.S. Environmental Protection Agency, 937 F. 2d 649 (D.C. Cir. 1991).

While neither the are rules, This principle has been applied to hold that agency 'clarification', such as the Statement of Interpretation, the "Reporting Guide" nor the April 1992 amendments will not applied retroactively.

> ...a federal court will not retroactively apply an unforeseeable interpretation of an administrative regulation to the detriment of a regulated party on the theory that the post hoc interpretation asserted by the Agency is generally consistent with the policies underlying the Agency's regulatory program, when the semantic meaning of the regulations, as previously drafted and construed by the appropriate agency, does not support the interpretation which that agency urges upon the court.

Standard Oil Co. v. Federal Energy Administration, 453 F. Supp. 203, 240 (N.D. Ohio 1978), aff'd sub nom. Standard Oil Co. v. Department of Energy, 596 F.2d 1029 (Em. App. 1978):

The 1978 Statement of Interpretation does not provide adequate notice of, and indeed conflicts with, the Agency's current position at §8(e) requires reporting of all 'positive' toxicological findings without regard to an assessment of their relevance to human health. In accordance with the statute, EPA's 1978 Statement of Interpretation requires the regulated community to use scientific judgment to evaluate the significance of toxicological findings and to determining whether they reasonably support a conclusion of a substantial risk. Part V of the Statement of Interpretation urges persons to consider "the fact or probability" of an effect's occurrence. Similarly, the 1978 Statement of Interpretation stresses that an animal study is reportable only when "it contains reliable evidence ascribing the effect to the chemical." 43 Fed Reg. at 11112. Moreover, EPA's Statement of Interpretation defines the substantiality of risk as a function of both the seriousness of the effect and the probability of its occurrence. 43 Fed Reg 11110 (1978). Earlier Agency interpretation also emphasized the "substantial" nature of a §8(e) determination. See 42 Fed Reg 45362, 45363

(1977). [Section 8(e) findings require "extraordinary exposure to a chemical substance...which critically imperil human health or the environment"].

The recently issued "Reporting Guide" and April 1992 Amendment guidance requires reporting beyond and inconsistent with that required by the Statement of Interpretation. Given the statute and the Statement of Interpretation's explicit focus on substantial human or environmental risk, whether a substance poses a "substantial risk" of injury requires the application of scientific judgment to the available data on a case-by-case basis.

If an overall weight-of-evidence analysis indicates that this classification is unwarranted, reporting should be unnecessary under §8(e) because the available data will not "reasonably support the conclusion" that the chemical presents a substantial risk of serious adverse consequences to human health.

Neither the legislative history of §8(e) nor the plain meaning of the statute support EPA's recent lowering of the reporting threshold that TSCA §8(e) was intended to be a sweeping information gathering mechanism. In introducing the new version of the toxic substances legislation, Representative Eckhart included for the record discussion of the specific changes from the version of H. R. 10318 reported by the Consumer Protection and Finance Subcommittee in December 1975. One of these changes was to modify the standard for reporting under §8(e). The standard in the House version was changed from "causes or contributes to an unreasonable risk" to "causes or significantly contributes to a substantial risk". This particular change was one of several made in TSCA §8 to avoid placing an undue burden on the regulated community. The final changes to focus the scope of Section 8(e) were made in the version reported by the Conference Committee.

The word "substantial" means "considerable in importance, value, degree, amount or extent". Therefore, as generally understood, a "substantial risk" is one which will affect a considerable number of people or portion of the environment, will cause serious injury and is based on reasonably sound scientific analysis or data. Support for the interpretation can be found in a similar provision in the Consumer Product Safety Act. Section 15 of the CPSA defines a "substantial product hazard" to be:

> "a product defect which because of the pattern of defect, the number of defective products distributed in commerce, the severity of the risk, or otherwise, creates a substantial risk of injury to the public."

Similarly, EPA has interpreted the word 'substantial' as a quantitative measurement. Thus, a 'substantial risk' is a risk that can be quantified, *See,* 56 Fed Reg 32292, 32297 (7/15/91). Finally, since information pertinent to the exposure of humans or the environment to chemical substances or mixtures may be obtained by EPA through Sections 8(a) and 8(d) regardless of the degree of potential risk, §8(e) has specialized function. Consequently, information subject to §8(e) reporting should be of a type which would lead a reasonable man to conclude that some type action was required immediately to prevent injury to health or the environment.

Attachment

Comparison:

Reporting triggers found in the 1978 "Statement of Interpretation/ Enforcement Policy",43 Fed Reg 11110 (3/16/78) and the June 1991 *Section 8(e) Guide.*

TEST TYPE	1978 POLICY CRITERIA EXIST?	New 1991 GUIDE CRITERIA EXIST?
ACUTE LETHALITY		
Oral	N}	Y}
Dermal	N}	Y}
Inhalation (Vapors)	}[6]	}[7]
aerosol	N}	Y}
dusts/ particles	N}	Y}
SKIN IRRITATION	N	Y[8]
SKIN SENSITIZATION (ANIMALS)	N	Y[9]
EYE IRRITATION	N	Y[10]
SUBCHRONIC (ORAL/DERMAL/INHALATION)	N	Y[11]
REPRODUCTION STUDY	N	Y[12]
DEVELOPMENTAL TOX	Y[13]	Y[14]

[6] 43 Fed Reg at 11114, comment 14:
"This policy statements directs the reporitng of specifiec effects when unknown to the Administrator. Many routine tests are based on a knowledge of toxicity associated with a chemicalL unknown effects occurring during such a range test may have to be reported if they are those of concern tot he Agency and if the information meets the criteria set forth in Parts V and VII."

[7] Guide at pp.22, 29-31.

[8] Guide at pp-34-36.

[9] Guide at pp-34-36.

[10] Guide at pp-34-36.

[11] Guide at pp-22; 36-37.

[12] Guide at pp-22

[13] 43 Fed Reg at 11112
"Birth Defects" listed.

[14] Guide at pp-22

NEUROTOXICITY	N	Y[15]
CARCINOGENICITY	Y[16]	Y[17]
MUTAGENICITY		
In Vitro	Y}[18]	Y} [19]
In Vivo	Y}	Y}
ENVIRONMENTAL		
Bioaccumulation	Y}	N
Bioconcentration	Y}[20]	N
Oct/water Part. Coeff.	Y}	N
Acute Fish	N	N
Acute Daphnia	N	N
Subchronic Fish	N	N
Subchronic Daphnia	N	N
Chronic Fish	N	N
AVIAN		
Acute	N	N
Reproductive	N	N
Reprodcutive	N	N

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[15] Guide at pp-23; 33-34.

[16] 43 Fed Reg at 11112
"Cancer" listed

[17] Guide at pp-21.

[18] 43 Fed Reg at 11112; 11115 at Comment 15
"Mutagenicity" listed/ *in vivo* vs *invitro* discussed; discussion of "Ames test".

[19] Guide at pp-23.

[20] 43 Fed Reg at 11112; 11115 at Comment 16.

CAS #100-21-0
Chem: Terephthalic acid
Title: The Effects of Prolonged Feeding of Terephthalic Acid (TPA) to Rats
Date: 11/15/77
Summary of Effects: Stones in the urinary tract (also observed hyperplasia, papilloma, squamous metaplasia, transitional cell tumors or squamous cell carcinoma

U.S. Department of Agriculture
Agricultural Research Service
Foreign Research and Technical
Program Division

Final Report - P.L. 480

Total Amount of Grant	IL.178,570
Project No. FG-Is-175	Grant No. AIO-ADP-8
Name of Institution	The Hebrew University-Hadassah Medical School, Department of Experimental Medicine & Cancer Research, Jerusalem, Israel

Project Title: THE EFFECTS OF PROLONGED FEEDING OF TEREPHTHALIC ACID (TPA) TO RATS

Submitted by Professor Jack Gross

Signature of principal investigator

J. Gross

Jack Gross, M.D., Ph.D.

Authorized by

A Keynan

Prof. A. Keynan
Chairman, Research and Development
The Hebrew University, Jerusalem

DuPont 11-15-77

FINAL REPORT

THE EFFECTS OF PROLONGED FEEDING OF TEREPHTHALIC ACID (TPA) TO RATS

GRANT NO. AIO-ADP-8

SUBMITTED BY JACK GROSS

PROFESSOR A. KEYNAN, CHAIRMAN
AUTHORITY FOR RESEARCH AND DEVELOPMENT

Experimental Methods

Eight groups of rats of the Wag/Rij (Wistar) strain were set up. There were 4 groups of females and 4 groups of males. Within each set of 4 groups the feeding procedure was respectively as follows: Ambar rat chow alone, and Ambar chow supplemented with 1%, 2% and 5% Terephthalic acid for two years. The animals were housed two to a translucent plastic cage and kept under specific pathogen-free (SPF) conditions.

The animals were examined daily, weighed weekly for the first three months and bi-weekly thereafter. Those found to be moribund or dead were submitted to autopsy and histopathological examination. The following tissues were taken routinely for histological examination: pituitary, thyroid, adrenal, heart, liver, lung, kidney, bladder, bone marrow, stomach, small intestine, pancreas and submaxillary gland. Additional tissues were taken where indicated.

Some of the tissues were weighed; all were fixed in Bouin's fluid, and imbedded in paraffin. Some animals could not be examined histologically because of advanced autolysis or destruction of the body through cannibalism.

At the time of sacrifice, blood was taken from the inferior vena cava for hematological studies and roughly quantitative urea determinations (Azostix$^{(R)}$, Ames Laboratories, Elkhart.)

The TPA used was obtained from BDH, England. The material was analyzed through the courtesy of Dr. Herbert G. Luther of Pfizer International, Inc., U.S.A., and showed a TPA content of 97.3% $\pm$ 0.8.

Various phases of this were carried out by the following, in addition to the principal investigator:

Investigators :-	% Time
Dr. Marianne Bloch	35
Dr. Norman Grover	10
Laboratory technicians :-	
Mr. Tibor Horkany	100
Mrs Esther Shvili	80
Animal technician :-	
Mr. Bendar Avidani	100

TPA groups, while in the male this was true only for the 2% and 5% groups. (b) The kidney weighed significantly less in the 1% and 2% groups of both sexes. (c) The heart was lighter in the 2% and 5% groups of both sexes. (d) The spleen was decreased in weight only in the male in the 2% and 5% group (e) The submaxillary gland weighed less in the combined 5% level. (f) The adrenal was heavier in the male 5% group while in this group the testis was reduced in size.

Taking into account the variation in body weights and the effect of TPA on growth (Table 1), organ weight relative to body weight was calculated (Table 3). The picture is somewhat different from that described above. In the females the relative weights of liver, kidney and heart in the 1% and 2% TPA groups are less than the controls. The adrenal weight was significantly increased in the 5% group. In the males the kidney was smaller in the 1% group and relatively enlarged in the 5% group. Also the heart and the adrenal were heavier than controls in the 5% group.

Results

1a. Effect on growth

During the course of the study an analysis of the weight curves was developed. The complete description of the analysis is given in a paper published in Growth which is appended as Appendix 1. This analysis at about 40 weeks of the experiment indicated that 2% and 5% TPA in the diet affected the parameters of growth and were an indication of toxicity. TPA at a level of 1% in the food had no effect. This projection is borne out in part by weights of the groups at the end of the Experiment (Table 1). With 2% and 5% TPA there was a significant depression in the body weight of the male groups; in the case of the females only 5% TPA significantly decreased body weight.

Table 1. Effect of TPA on Body Weight

Group	Female M ± S.E.	N	Male M ± S.E.	N
Control	190.2 ± 5.6	40	331.1 ± 9.1	34
1% TPA	188.6 ± 4.0	38	330.6 ± 9.3	32
2% TPA	181.3 ± 3.9	42	298.7** ± 6.9	40
5% TPA	151.8** ± 3.3	20	257.8** ± 7.8	17

Significance of Difference from Control

**) = 1%

1b. Effects on organ weights

The data on selected organ weights is given in Tables 2 and 3. In terms of absolute organ weights, the following differences were found. (Table 2). (a) The liver was significantly lighter in weight in the female - 1%, 2% and 5%

Table 3. Effect of TPA on Relative Organ Weight

Females

mg/100 g BW Mean ± S.E.

Organ	Control	1% TPA	2% TPA	5% TPA
No. animals :	40	38	42	20
Liver	4173 ± 146	3965 ± 92***	3673 ± 79***	4245 ± 128
Kidney	518 ± 24	418 ± 11***	419 ± 10***	587 ± 63
Heart	377 ± 10	353 ± 7*	343 ± 5***	390 ± 10
Spleen	206 ± 12	213 ± 13	189 ± 4	248 ± 29
Submax. gl.	98 ± 3.4	96 ± 2.5	100 ± 2.1	100 ± 3.4
Adrenal	12 ± 0.7	11 ± 0.4	11 ± 0.4	16 ± 0.6*

Males

No. animals :	34	32	40	17
Liver	2981 ± 74	2906 ± 74	2923 ± 94	3150 ± 121
Kidney	381 ± 12	351 ± 9	368 ± 12	472 ± 24***
Heart	296 ± 7	287 ± 7	293 ± 7	326 ± 10**
Spleen	163 ± 5	154 ± 5	151 ± 7	165 ± 13
Submax. gl.	69 ± 2.6	66 ± 1.9	70 ± 1.7	73 ± 25
Adrenal	7.3 ± 0.47	7.0 ± 0.37	8.2 ± 0.39	12.1 ± 1.2**
Testis	571 ± 17	585 ± 19	601 ± 18	646 ± 35

* P < 5%

** P < 2%

*** P < 0.1%

Table 2. Effect of TPA on Absolute Organ Weight

Females

mg Mean ± S.E.

Organ	Control	1% TPA	2% TPA	5% TPA
No. animals:	40	38	42	20
Liver	7950 ± 350	6950 ± 200**	6650 ± 190***	6430 ± 210***
Kidney	961 ± 35	776 ± 14***	748 ± 13***	877 ± 85
Heart	704 ± 19	659 ± 14	616 ± 10***	588 ± 12***
Spleen	389 ± 21	407 ± 31	341 ± 10	375 ± 44
Submax. gl.	182 ± 5	179 ± 4	178 ± 3	153 ± 5
Adrenal	22 ± 1.0	20 ± 0.7	20 ± 0.6	24 ± 0.7

Males

No. animals:	34	32	40	17
Liver	9938 ± 407	9708 ± 447	8733 ± 329*	8201 ± 486***
Kidney	1239 ± 31	1143 ± 29*	1078 ± 23***	1205 ± 57
Heart	904 ± 17	937 ± 23	877 ± 17***	839 ± 38***
Spleen	538 ± 20	516 ± 25	455 ± 23***	433 ± 40*
Submax. gl.	277 ± 9	218 ± 8	209 ± 7	188 ± 8***
Adrenal	23 ± 0.9	22 ± 0.8	24 ± 0.9	31 ± 3**
Testis	1860 ± 34	1906 ± 58	1772 ± 46	1712 ± 61*

* P < 5%

** P < 2%

*** P < 0.1%

2. Survival

The toxicity of TPA as indicated above might express itself on survival. The data are given in Table 4, from which it can be seen that fewer animals from the 5% group survived the 24 month feeding period. Statistica analysis using Chi square shows that the difference is significant at p < for females and at p < 5% for males.

Cumulative mortality curves with time are shown in Figure 1. The curves for the 1% and 2% groups do not differ appreciably from those of the controls. The curves begin their upward trend about the 19th month. With 5% group the mortality trend begins at about the second month and rises ste ily during the course of the experiment.

Table 4. Effect of TPA on Survival

Animals surviving 24 months:

Group	Female	Male
Control	37/50	33/50
1% TPA	38/50	26/50
2% TPA	42/50	37/50
5% TPA	15/50	16/50

3. Hematological Parameters

The data for hemoglobin, red blood cell and white blood cell conce trations are given in Table 5. There is no effect of TPA feeding on any of these parameters. Equally, histological examination of the bone marrow sho no changes between the various groups.

TPA groups, while in the male this was true only for the 2% and 5% groups. (b) The kidney weighed significantly less in the 1% and 2% groups of both sexes. (c) The heart was lighter in the 2% and 5% groups of both sexes. (d) The spleen was decreased in weight only in the male in the 2% and 5% group (e) The submaxillary gland weighed less in the combined 5% level. (f) The adrenal was heavier in the male 5% group while in this group the testis was reduced in size.

Taking into account the variation in body weights and the effect of TPA on growth (Table 1), organ weight relative to body weight was calculated (Table 3). The picture is somewhat different from that described above. In the females the relative weights of liver, kidney and heart in the 1% and 2% TPA groups are less than the controls. The adrenal weight was significantly increased in the 5% group. In the males the kidney was smaller in the 1% group and relatively enlarged in the 5% group. Also the heart and the adrenal were heavier than controls in the 5% group.

Table 5. Effect of TPA on Blood Picture

Mean ± S.E.

	FEMALES				MALES			
	N	Hgb	RBC	WBC	N	Hgb	RBC	WBC
Control	39	15.4±0.4	9.6±0.5	7.2±0.7	29	17.4±0.3	9.9±0.4	6.5±0.7
1% TPA	36	14.6±0.3	8.6±0.3	5.8±0.4	29	17.3±0.3	9.3±0.4	7.6±0.6
2% TPA	42	15.1±0.3	8.8±0.3	6.7±0.5	37	16.2±0.5	10.2±0.4	6.6±0.5
5% TPA	12	15.2±0.6	9.2±0.5	6.8±1.0	13	16.2.0.6	8.9±0.6	8.5±1.6

Hgb = Hemoglobin (g/100 ml)

RBC = Red Blood Cells (millions / mm^3)

WBC = White blood Cells (thousands / mm^3)

4. Pathological Findings

The predominant cause of death in all the groups was the development of a tumor of the pituitary (Fig. 2). This was an adenomatous growth containing large hemorrhagic lakes (Fig. 3) and could reach diameters of the order of 1 cm. Microscopically (Fig. 4) it showed the characteristics of a chromophobe adenoma. In some cases the nuclei were large and highly pleomorphic.

The main cause of death in the TPA fed animals was due to the formation of stones of TPA in the urinary tract (Figs. 8-13). This occurred almost exclusively in the 5% group (Table 6) and resulted in changes in the urinary tract and kidney nephropathy (Table 6) which will be described below. The stones found in the bladder varied in size from gravel (Figs. 10-11) through larger and larger concretions (Figs. 8-9) to single large stones completely

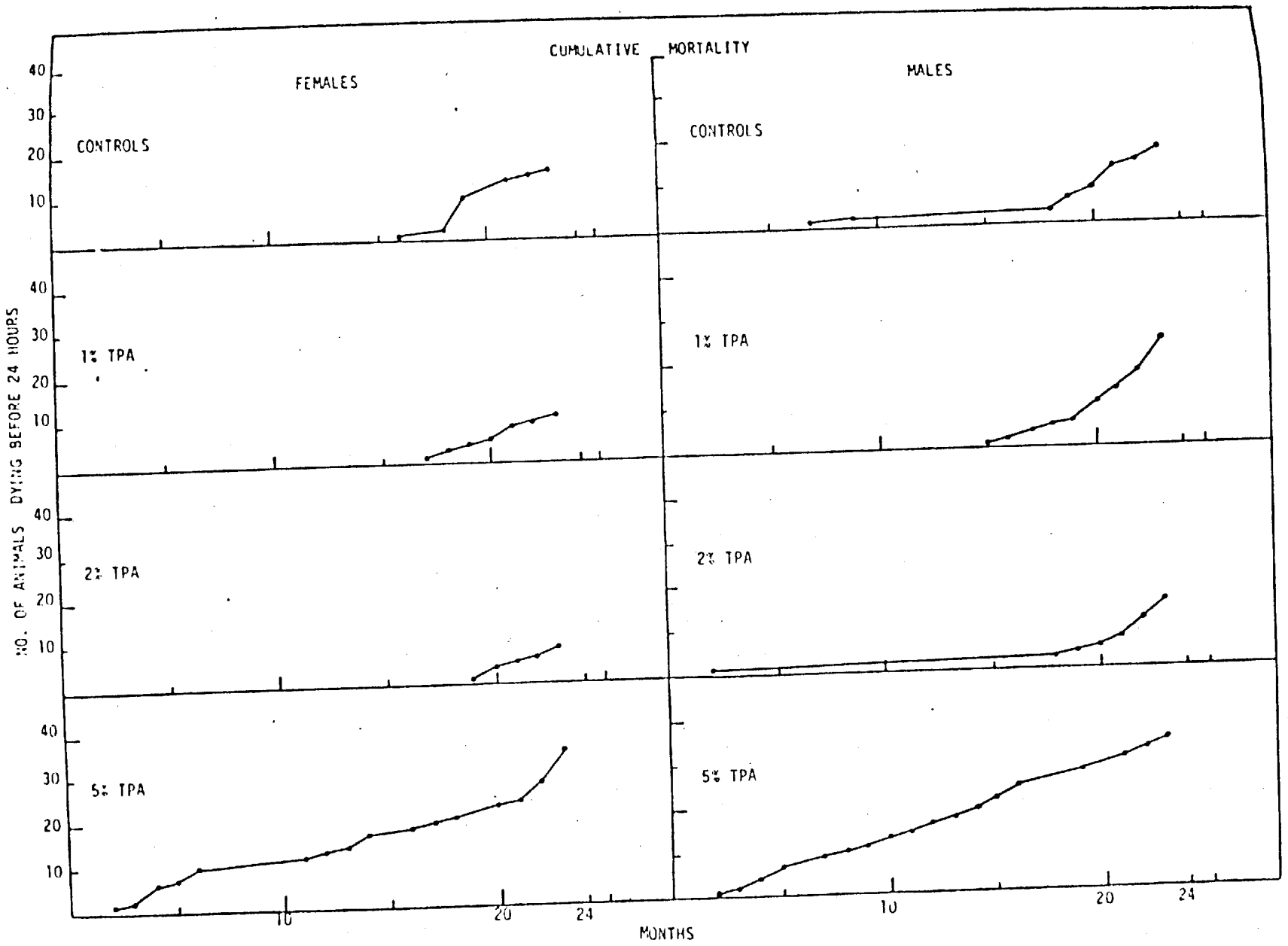

CUMULATIVE MORTALITY
FEMALES
MALES
CONTROLS
CONTROLS
1% TPA
1% TPA
2% TPA
2% TPA
5% TPA
5% TPA
NO. OF ANIMALS DYING BEFORE 24 HOURS
40
30
20
10
10
20
24
MONTHS

PLATE II

FIG. 8 MACROSCOPIC VIEW OF THE URINARY SYSTEM OF A FEMALE RAT ON 5% TPA ON THE DIET FOR SIXTEEN MONTHS. NOTE THE DISTENDED IRREGULAR BLADDER (B) AND THE DILATED URETER ON THE LEFT SIDE (U).

FIG. 9 THE OPEN BLADDER OF FIGURE 8 IS FILLED WITH NUMEROUS STONES OF VARIOUS SIZES.

FIG. 10 THIS IS SIMILAR TO FIGURE 8 AND SHOWS A FEMALE ANIMAL FED FOR 24 MONTHS ON 5% TPA. NOTE THE ENLARGED BLADDER (B) AND THE IRREGULAR SURFACE OF THE RIGHT KIDNEY (K).

FIGS 11 AND 13 SHOW THE PRESENCE OF FINE GRAVEL FILLING THE URINARY BLADDER AND THE ENLARGED PELVIS OF TH KIDNEY.

FIG. 12 THIS SHOWS THE LARGEST BLADDER STONE FOUND. IT WAS PRESENT IN A FEMALE RAT FED 5% TPA. THE ANIMAL DIED AT 22 MONTHS OF FEEDING.

PLATE I

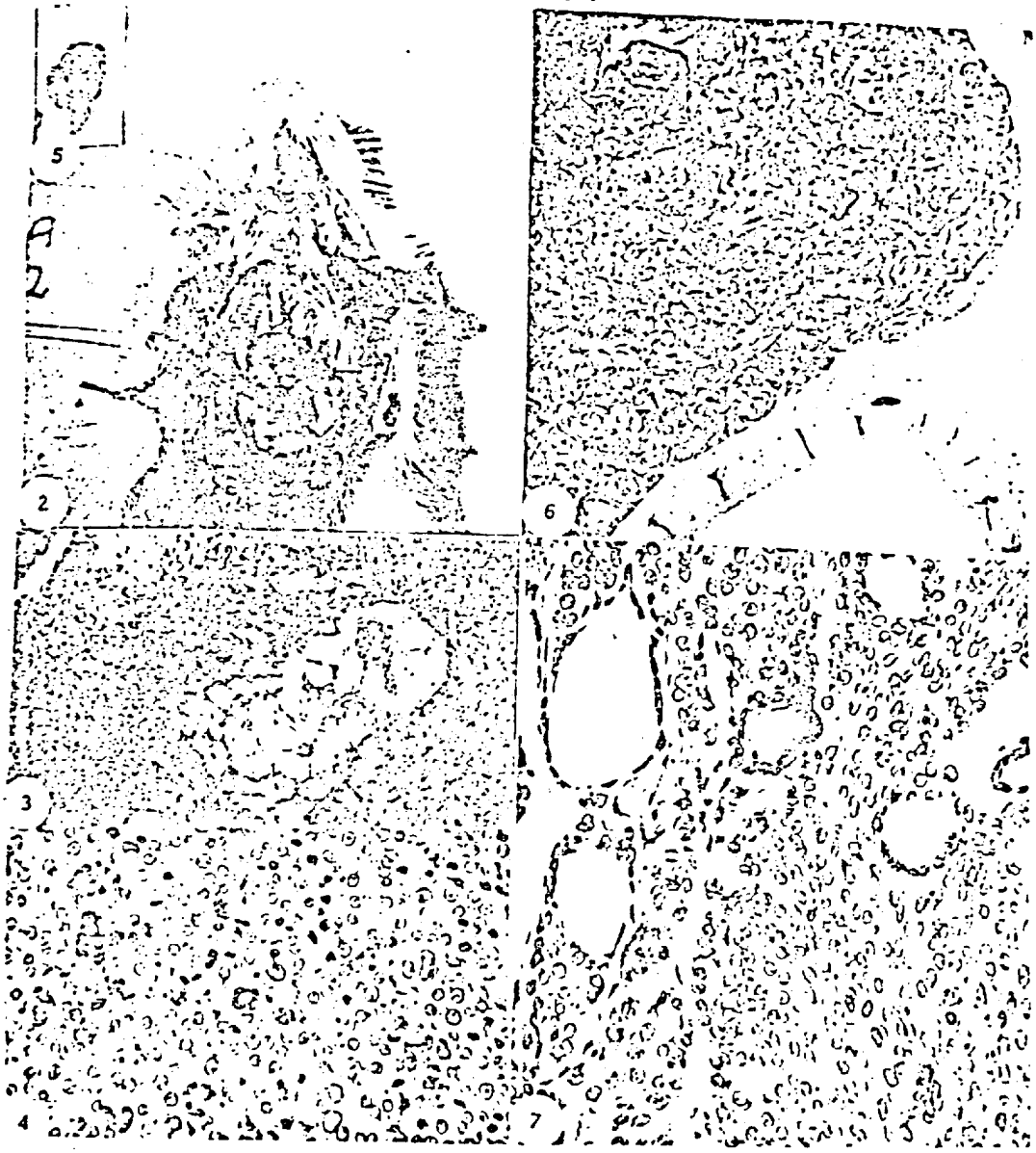


FIG. 2 VIEW INTO THE BASE OF THE SKULL OF A MALE RAT FED 5% TPA FOR EIGHTEEN MONTHS. NOTE THE TUMOR OF THE PITUITARY (T). x 1.2

FIG. 3 SECTION THROUGH THE PITUITARY TUMOR. NOTE SOLID TISSUE SURROUNDING HEMORRHAGIC LAKES. x 90

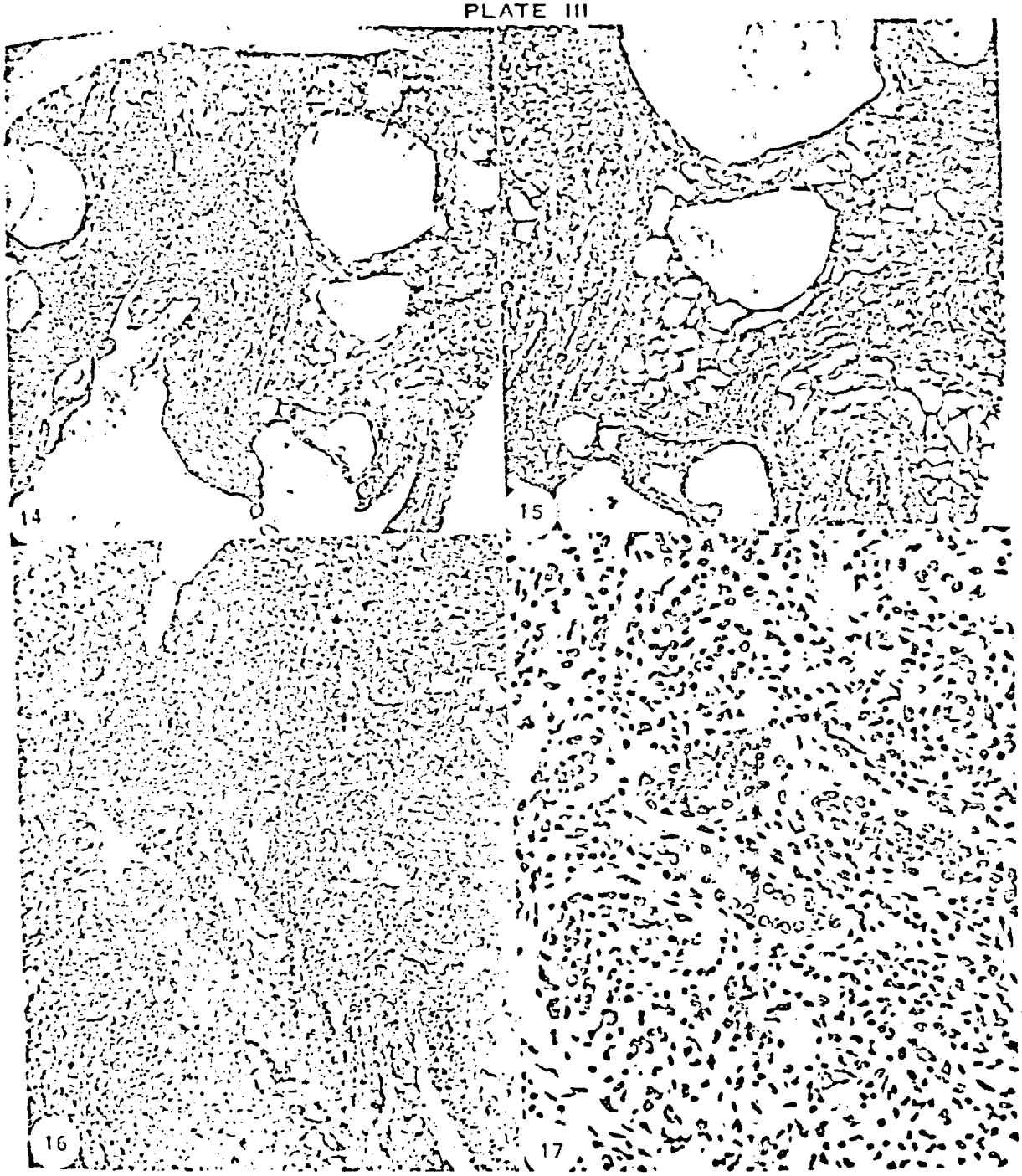
FIG. 4 SECTION THROUGH THE SOLID PORTION OF THE PITUITARY TUMOR. NOTE THE PLEOMORPHIC NUCLEI AND THE LACK OF GRANULES IN THE CYTOPLASM. x 360

FIG. 5 TRACHEA AND THYROID LOBES FROM A FEMALE CONTROL RAT 24 MONTHS OF AGE. NOTE THE RIGHT LOBE OF THE THYROID IS MARKEDLY ENLARGED. x 1.2

FIG. 6 SECTION THROUGH THE ENLARGED THYROID LOBE. THE LOBE IS FILLED WITH MASSES OF SOLID TISSUE REPLACING MOST OF THE FOLLICLES. x 36

FIG. 7 HIGH POWER VIEW OF AN AREA FROM FIG. 6. x 360 THERE ARE MASSES OF LARGE PALE POLYHEDRAL CELLS. THESE HAVE BEEN IDENTIFIED AS MEDULLARY CARCINOMA. (BOORMAN, VAN NOORD AND HOLLANDER, 1971).

PLATE III



FIGS 14 AND 15 A SECTION FROM THE KIDNEY OF A 5% TPA FEMALE WITH BLADDER STONES SURVIVING 24 MONTHS. THE MAGNIFICATIONS ARE x36 AND x 90, RESPECTIVELY. NOTE THE DILATED PELVIS AND TUBULES WITH FORMATION OF APT LIKE STRUCTURES. THE NORMAL ARCHITECTURE OF THE KIDNEY IS ALMOST TOTALLY GONE.

FIGS 16 AND 17 SECTION FROM THE KIDNEY OF A MALE RAT DYING AFTER 14 MONTHS ON A 5% TPA DIET. BLADDER STONES WERE PRESENT. THE MAGNIFICATIONS ARE x 90 AND x 360 RESPECTIVELY. THERE IS EVIDENCE OF REPLACEMENT OF KIDNEY STRUCTURE BY A CHRONIC INFLAMMATORY PROCESS I.E. PYELONEPHRITIS.

filling and distending the urinary bladder (Fig. 12). Stones were also found in the pelvis of the kidney (Fig. 13).

Table 6. TPA Feeding on the Formation of Stones in the Urinary Tract and the Incidence of Nephropathy

	Females		Males	
	Stones	Nephropathy	Stones	Nephropathy
Controls	0% (46)	0% (46)	0% (45)	0% (45)
1% TPA	2% (48)	0% (48)	0% (48)	2.3% (43)
2% TPA	0% (50)	2.1% (47)	0% (50)	0% (48)
5% TPA	93% (42)	80% (34)	89% (47)	87% (37)

( ) no. of animals in group

The kidneys showed varying degrees of destruction from focal areas (Fig. 16) to almost complete obliteration of the kidney structure (Figs. 14 & 15). This was associated with an infiltration of inflammatory cells and in fact indicated various degrees of pyelonephritis (Figs. 16 & 17). In a number of cases, perinephritis was also found where the inflammatory cell infiltration in the connective tissue and between the fat cells in the pelvis of the kidney was easily seen. In a few cases basophilic material was found in the papillae. It is likely that this material is precipitated TPA. This was associated with papillary necrosis.

These changes in the kidneys resulted in changes in the blood urea (Table 7). The data showed that in the 5% groups the urea content of the blood was significantly higher than in the other groups and reached levels, in some cases, exceeding 100 mg %.

PLATE IV

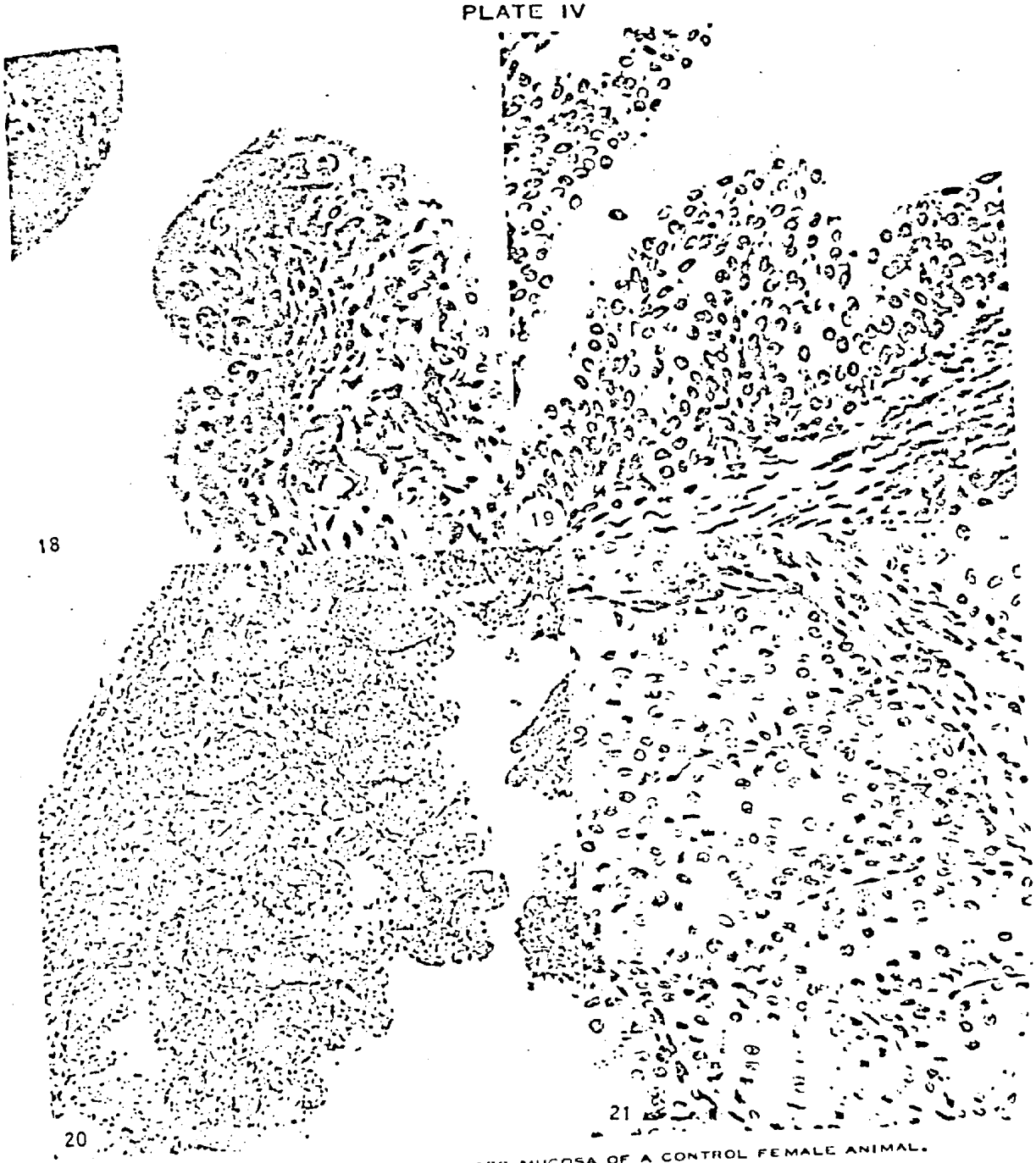


FIG. 18 A SECTION THROUGH THE BLADDER MUCOSA OF A CONTROL FEMALE ANIMAL. x 360
NOTE THE EPITHELIUM CONSISTS OF 3 – 4 CELL LAYERS.

FIGS 19, 20 AND 21 SECTIONS FROM THE URINARY TRACT OF A FEMALE ANIMAL WITH STONES ON 24 MONTHS OF 5% TPA IN THE DIET. x 360

FIG. 19 IS A SECTION THROUGH THE PELVIS SHOWING A MARKED HYPERPLASIA OF THE EPITHELIUM (COMPARE WITH FIG. 18) x 360

FIG. 20 THE BLADDER MUCOSA SHOWS AN HYPERPLASIA WITH THE FORMATION OF A PAPILLOMA x 36

FIG. 21 A HIGHER MAGNIFICATION x 360 FROM THE SECTION IN FIG. 20 SHOWS THE HIGH DEGREE OF PROLIFERATION OF THE TRANSITIONAL CELLS INTO PSEUDO-GLANDULAR STRUCTURES. x 360

Table 7. Effect of TPA on Blood Urea

Per cent of animals with 40 mg % or greater

		Females		Males
Controls	42	5%	40	17%
1% TPA	41	7%	41	10.0%
2% TPA	45	4%	45	4.0%*
5% TPA	27	26%***	22	23%**

*) < 5% Significance determined by Chi Square

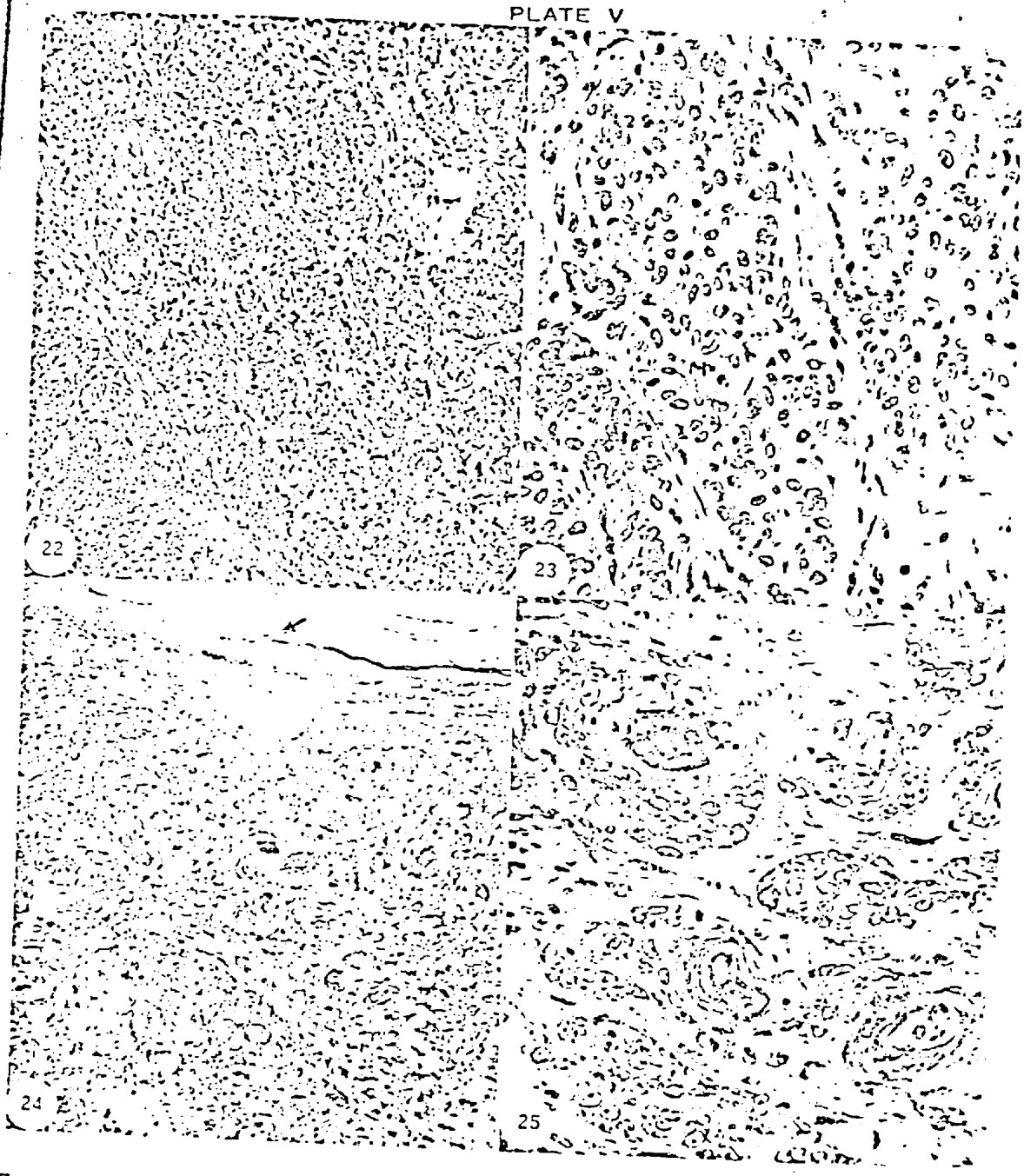
**) < 2%

***) < 0.1%

A striking and consistent finding was hyperplasia of the pelvis and/or ureteral and/or bladder epithelium in the 5% group. The normal appearance of the mucosa is shown in Fig. 18. This can be compared to the hyperplastic epithelium shown in Fig. 19. The hyperplasia may develop into a papilloma (Fig. 20), which on higher magnification shows a pseudo glandular appearance (Fig. 21). This can progress into an infiltrating transitional cell tumor (Fig. 22) which shows numerous mitoses (Fig. 23) among the clumps of cells. In some cases the epithelium will show squamous metaplasia (Fig. 24) with the development of a florid squamous cell carcinoma (Figs. 24-25). The frequency of occurrence of changes from hyperplasia to tumor is shown in Tables 8 and 9. These pathological changes are almost solely confined to the 5% group. Individual cases are found in the 1% and 2% groups and none are found in the control groups.

Tables 8 and 9 also indicate the incidence of a number of other tumors, none of which seem to predominate in the TPA fed groups. The most common tumor is the pituitary adenoma previously described (Figs, 2, 3, 4). The next commonest tumor is that of the thyroid. This tumor can grow to a relatively large size (Figs. 5 & 6). In most cases it has a solid adenomatous structure which infiltrates between and replaces the normal follicles. This is most likely a medullary carcinoma arising from the c cells (Boorman, Van Noord and Hollander, 1971). In some cases this tumor showed local invasion. The next tumor in order of frequency is the mammary tumor in the female. This may show a glandular appearance as on Fig. 26. On closer examination the cells may show vacuolation (Fig. 27) as if they were under the influence of a secretory hormone such as prolactin. These areas may be interspersed with frankly papillary structures (Fig. 28). There are also tumors which have a solid anaplastic looking structure (Fig. 29).

PLATE V



FIGS 22 AND 23 SECTIONS THROUGH A BLADDER TUMOR IN A FEMALE RAT 24 MONTHS ON TPA AND HAVE STONES IN THE BLADDER.

FIG. 22 A TRANSITIONAL CELL CANCER INVADING THE WALL OF THE BLADDER. x 90

FIG. 23 A HIGHER POWER VIEW OF FIG. 22, SHOWING THE CELLS WITH SEVERAL MITOSES (M) x 360

FIGS 24 AND 25 SECTIONS THROUGH A BLADDER TUMOR, FEMALE RAT, 24 MONTHS, TPA WITH BLADDER STONES.

FIG. 24 NOTE THE SQUAMOUS METAPLASIA (ARROW) OF THE EPITHELIUM WITH AN INFILTRATION SQUAMOUS CELL CARCINOMA EVIDENT, x 36

FIG. 25 HIGHER MAGNIFICATION OF FIG. 24 SHOWING THE CHARACTERISTIC STRUCTURE OF SQUAMOUS CELL CARCINOMA. x 360

Table 8. TPA Feeding and Tumor Incidence

	Females			
		TPA		
Tumor of	Control	1%	2%	5%
Pituitary	33/46	36/48	37/47	14/34
Thyroid	19/46	14/48	18/47	7/34
Mammary gland	11/46	8/48	8/47	1/34
Adrenal medulla	2,46	2/48	0/47	0/34
Parathyroid	1/46	0/48	0/47	0/34
Connective tissue	1/46	2/48	1/47	1/34
Liver	0/46	0/48	2/47	0/34
Lung	0/46	1/48	1/47	1/34
Leukemia	0/46	1/48	0/47	0/34
Ovary	0/46	1/48	0/47	1/34
Uterus	0/46	0/48	0/47	1/34
Bladder & Ureter	0/46	0/48	2/47	21/34

PLATE VI

FIGS 26 AND 27 MAMMARY TUMOR IN A FEMALE CONTROL RAT 24 MONTHS OF AGE.

FIG. 26 SOLID AREAS OF TUMOR WHICH ALSO CONTAINED NECROTIC AREAS. x 90

FIG. 27 GLANDULAR APPEARANCE, THE CELLS SHOW MARKED VACUOLATION AS IF UNDER HORMONAL STIMULUS. x 360

FIGS 28 AND 29 MAMMARY TUMOR IN A FEMALE CONTROL RAT WHICH SURVIVED 20 MONTHS.

FIG. 28 AN AREA OF THE TUMOR SHOWING AN AREA OF VACUOLATED GLANDULAR CELLS MERGING INTO A PAPILLARY FORMATION. x 360

FIG. 29 IN ANOTHER AREA OF THE SAME TUMOR THERE ARE SOLID MASSES OF ANAPLASTIC-LOOKING CELLS. x 360

The other tumors found occur with a low frequency. They are illustrated as follows. The liver tumors found were all hamartomas as illustrated in Fig. 30. The lung tumors were small nodules of fusiform and foamy cells as in Fig. 31. The mesenchymal tumors were sarcomas showing active division (Figs. 32 & 35). A single small nodule was found in one kidney. It appears to be composed of cells resembling those of the distal tubule (Fig. 23). Pheochromocytomas were found. They grew in dimensions that much enlarged the adrenal and compressed the cortex (Figs. 36, 37). Tumors of the genital tract were also not uncommon. These included granulosa cell tumors of the ovary (Fig. 34), sarcoma of the uterus (Fig. 35), adenocarcinoma of the prostate (Fig. 38) and the seminal vesicle (Figs. 40 & 41), mesothelioma of the epididymis (Fig. 39) and interstitial cell tumors of the testis (Figs. 42 & 43).

The incidence of tumor types is virtually the same as that found by Boorman and Hollander (1971) in the same strain of rats (Table 10).

Table 10. Per Cent of Animals with Spontaneous Neoplams in Wag/Rij Females

	B & H	This study
Chromophobe adenoma	69%	72%
Medullary thyroid carcinoma	40%	41%
Mammary tumors	25%	24%
Pheochromocytoma	2%	2%
Mesenchymal tumors	2%	2%

Table 9. TPA Feeding and Tumor Incidence

Males

Tumor of	Control	TPA 1%	TPA 2%	TPA 5%
Pituitary	36/45	37/43	43/48	21/37
Thyroid	19/45	14/43	17/48	7/37
Adrenal Medulla	0/45	1/43	1/48	1/37
Connective Tissue	2/45	2/43	1/48	0/37
Liver	1/45	0/43	0/48	0/37
Lung	2/45	3/43	0/48	0/37
Leukemia	0/45	1/43	0/48	0/37
Genital Tract	1/45	6/43	2/48	1/37
Kidney	0/45	1/43	0/48	0/37
Bladder & Ureters	0/45	1/43	1/48	2/37
Pancreatic Islet	1/45	0/43	0/48	0/37

PLATE VII

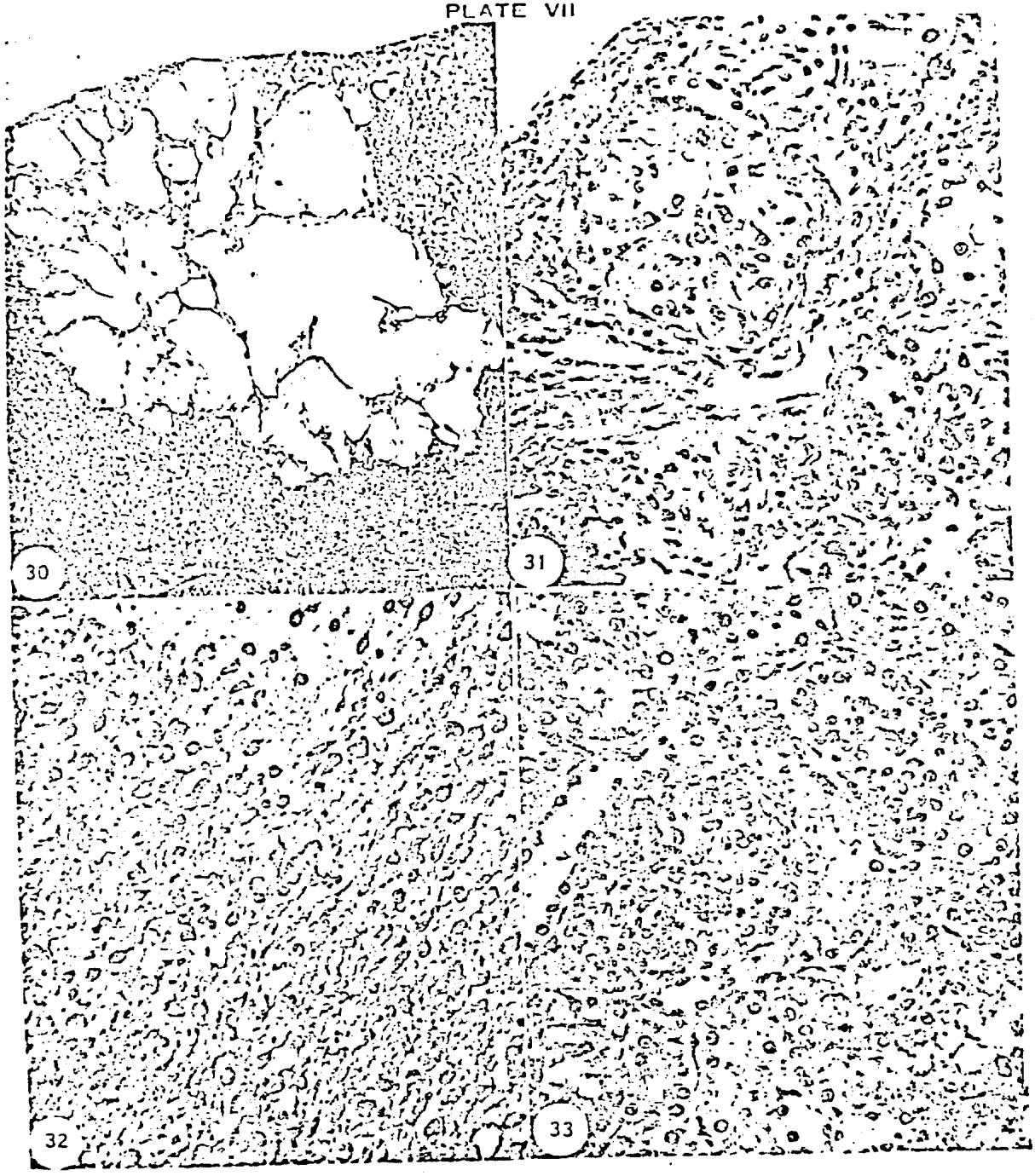


FIG. 30 LIVER TUMOR, HAMARTOMA, IN A FEMALE CONTROL RAT, 24 MONTHS OF AGE. x 90

FIG. 31 LUNG TUMOR IN MALE RAT ON 2% TPA DIET, 24 MONTHS OLD. THE TUMOR IS COMPOSED OF VACUOLATED (FOAM CELLS) AND SPINDLE LIKE CELLS. x 360

FIG. 32 SECTION FROM A LARGE SUBCUTANEOUS TUMOR AROUND THE ANAL AREA IN A CONTROL FEMALE x 360

NOTE THE MESENCHYMAL CHARACTER OF TIE TISSUE. A MULTIPOLAR MITOSIS IS PRESENT IN THE CENTER OF THE FIELD (ARROW) x 360

FIG. 33 SMALL MICROSCOPIC TUMORS OF THE KIDNEY. x 360

PLATE VIII

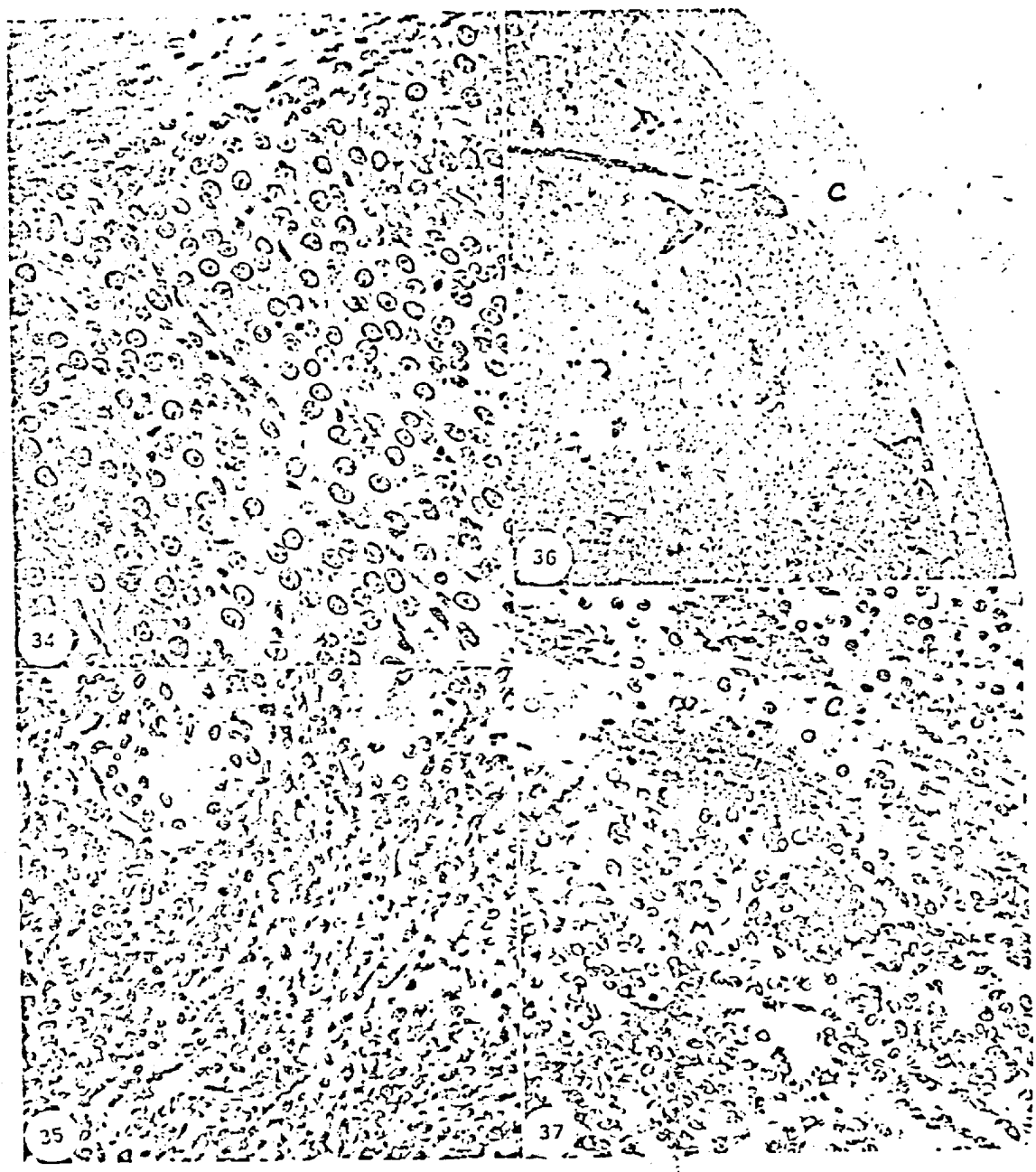
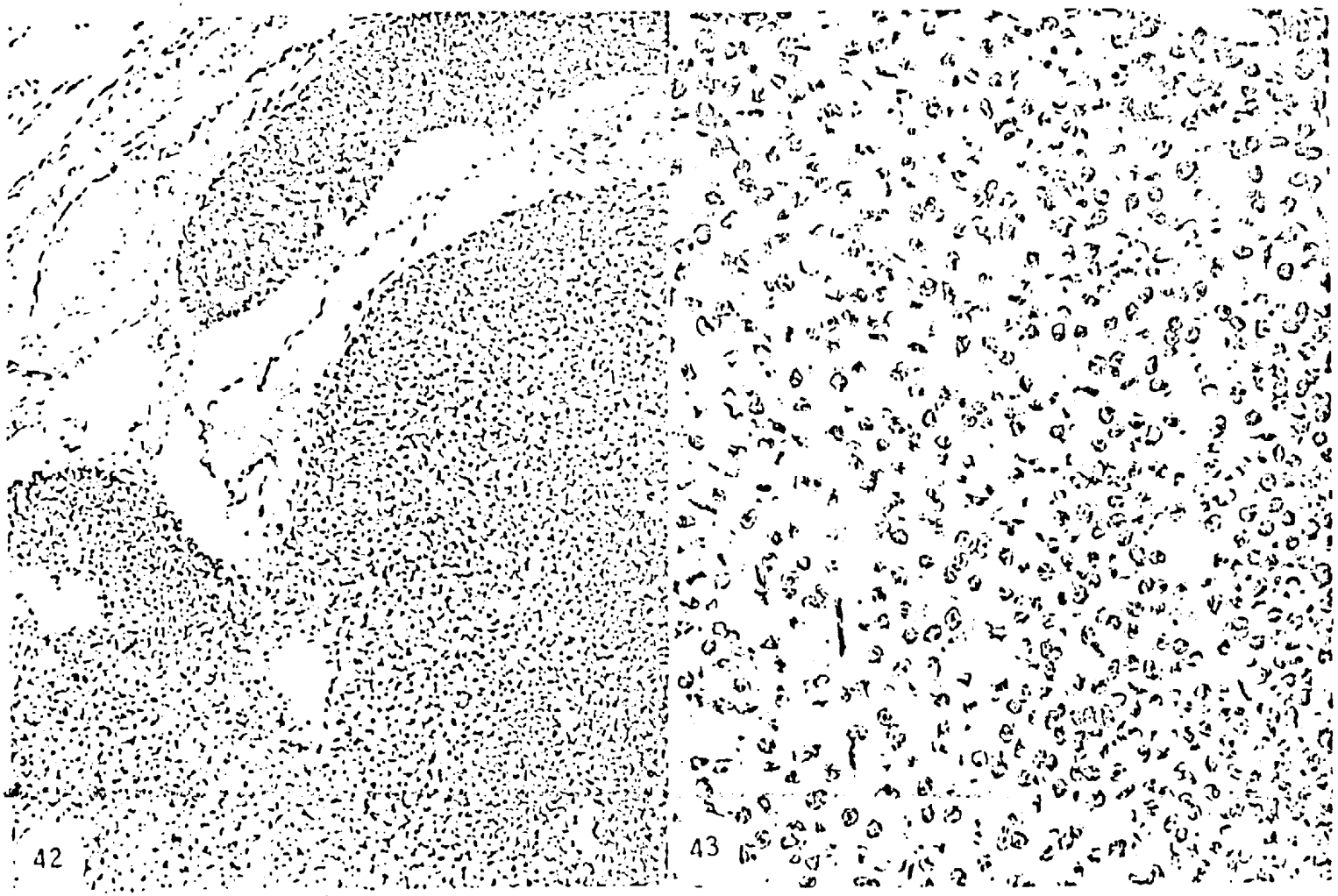


FIG. 34 SECTION FROM A LARGE TUMOR OF THE OVARY IN A FEMALE RAT ON A DIET OF 1% TPA. THE STRUCTURE IS TYPICAL OF A GRANULOSA CELL TUMOR. x 360

FIGS 36 AND 37 SECTIONS FROM A TUMOR OF THE ADRENAL WITH A DIAMETER OF 1 CM. THE TUMOR WAS PRESENT IN A MALE RAT ON A 2% TPA DIET FOR 24 MONTHS.
FIG. 36 THE CORTEX (C) IS COMPRESSED INTO A NARROW RIM AROUND A MUCH ENLARGED MEDULLA, x 90
FIG. 37 HIGHER MAGNIFICATION AT THE MARGIN OF THE CORTEX (C) WITH THE MEDULLA (M). THE MEDULLA SHOWS THE CHARACTERISTICS OF A PHAEOCHROMACYTOMA. x 360

FIG. 35 SECTION FROM UTERINE TUMOR IN FEMALE RAT ON 5% TPA FOR 18 MONTHS. THE SECTION SHOWS INFILTRATION OF THE WALL OF URINARY BLADDER BY THE MESENCHYMAL TUMOR. x 360

PLATE X



FIGS 42 AND 43 INTERSTITIAL TUMOR OF THE TESTES IN A RAT ON 5% TPA FOR 24 MONTHS.

FIG. 42 SHOWS THE TUMOR COMPRESSING THE TUBULAR TISSUE OF THE ORGAN x 90

FIG. 43 HIGHER MAGNIFICATION OF THE TUMOR x 360

PLATE IX

FIG. 38 ADENOCARCINOMA OF THE PROSTATE IN A RAT ON 2% TPA DIET FOR 19 MONTHS. × 90

FIG. 39 MESOTHELIOMA OF THE EPIDIDYMIS IN A RAT ON 2% TPA FOR 24 MONTHS. × 360

FIGS 40 AND 41 ADENOCARCINOMA OF THE SEMINAL VESICLE IN A RAT ON 2% TPA FOR 24 MONTHS.
FIG. 40 × 90. FIG. 41 × 360.

Is there any influence of TPA feeding on tumor incidence. From inspection it would appear that except for tumors of the urinary tract, 5% TPA feeding decreases the incidence of spontaneous tumors. This was analyzed in Table 11.

Table 11. TPA Feeding on Incidence of Spontaneous Tumors

	Females	Males
Controls	66/46	62/45
1% TPA	65/43	65/43
2% TPA	67/47	64/48
5% TPA	26/34	30/37

The difference between the 5% TPA group of females and the controls is just above the 5% level for significance by Chi square. In the males there is no significant difference. Among the individual tumor types it could be shown that between the 5% TPA group and the controls, there was a significant decrease in the incidence of mammary tumors in the females, $< 5\% > 2\%$, and of thyroid tumors in the male ($p < 5\%$). It is interesting to note that Nagasawa and Fujimoto (1973) found that feeding 0.5% TPA to C3H mice inhibited spontaneous mammary tumorogenesis. In our series it is difficult to implicate TPA as the tumor inhibiting agent since neither the 2% or the 1% groups showed any significant trend toward tumor inhibition.

Summary of Significant Findings

1. TPA feeding inhibits growth at the 2% and 5% level in males and at the 5% level in females.

2. TPA causes a decrease in the relative weight of some organs. At the 1% level liver weight is decreased in the females and the kidney is relatively smaller in both sexes. At the 2% level the relative weight of the liver, kidney and heart are decreased only in the female group. At the 5% level there is a significant increase in kidney weight in the males and an increased adrenal weight in both sexes.

3. There was an increased mortality in the 5% TPA groups which begins about the 2nd month of feeding. 1% and 2% TPA feeding had no effect on survival.

4. The predominant cause of morbidity and mortality in the 5% group was due to the formation of TPA stones in the urinary tract. This occurred from the pelvis of the kidney to the urinary bladder. There was resultant hydronephrosis and pyelonephritis. The presence of stones causes changes in the epithelium of the urinary tract ranging through hyperplasia, papilloma, squamous metaplasia to both transitional cell tumors or squamous cell carcinomata. The incidence of nephropathy was also reflected by an increase in blood urea content.

5. TPA feeding did <u>not</u> cause an increased incidence of spontaneous tumors. In fact, in the 5% groups there was a significant decrease in mammary tumor incidence in the females and thyroid medullary carcinoma in the males.

References

Boorman, G.A., M.J. van Noord and C.F. Hollander. Ann. Rep. Radiobiol. Inst. TNO, 1971, Rijswik, The Nethertands, p. 137.

Boorman, G.A., and C.F. Hollander. Ann. Rep. Radiobiol. Inst. TNO, 1971, Rijswik, The Nethertands. p.142.

Nagasawa, H., and M. Fujimoto. Experienta, 29, (1973), 89.

6. TPA feeding at 1% of the diet or less had no demonstrable toxicity for rats of the Wag/Rij (Wistar) strain.

L

Triage of 8(e) Submissions

Date sent to triage: 2/5/96

NON-CAP CAP

Submission number: 13136A

TSCA Inventory: Y N D

Study type (circle appropriate):

Group 1 - Dick Clements (1 copy total)

ECO AQUATO

Group 2 - Ernie Falke (1 copy total)

ATOX SBTOX SEN w/NEUR

Group 3 - Elizabeth Margosches (1 copy each)

STOX CTOX EPI RTOX GTOX

STOX/ONCO CTOX/ONCO IMMUNO CYTO NEUR

Other (FATE, EXPO, MET, etc.): _____

Notes:

THIS IS THE ORIGINAL 8(e) SUBMISSION; PLEASE REFILE AFTER TRIAGE DATABASE ENTRY

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entire document: 0 (1) 2 **pages** 1, 1st tab **pages** 1, all tabs

Notes: 2-sided!

Contractor reviewer : LPS **Date:** 5/11/95

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ-0992-13136 SEQ. A

TYPE (INT) SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

SUB. DATE: 09/11/92 OTS DATE: 09/22/92 CSRAD DATE: 03/23/95

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
(0559) REFER TO CHEMICAL SCREENING
(0576) CAP NOTICE

VOLUNTARY ACTIONS:
(0401) NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKER PROTECTION
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP/U DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

CHEMICAL NAME: Terephthalic acid (TPA)

CASE: 100-21-0

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
(0202)	ONCO (ANIMAL)	01 (02) 04
0203	CELL TRANS (IN VITRO)	01 02 04
0204	MUTA (IN VITRO)	01 02 04
0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
0209	NEURO (ANIMAL)	01 02 04
0210	ACUTE TOX. (HUMAN)	01 02 04
0211	CHR. TOX. (HUMAN)	01 02 04
0212	ACUTE TOX. (ANIMAL)	01 02 04
0213	SUB ACUTE TOX (ANIMAL)	01 02 04
0214	SUB CHRONIC TOX (ANIMAL)	01 02 04
(0215)	CHRONIC TOX (ANIMAL)	01 (02) 04

INFORMATION TYPE:		P F C
0216	EPI/CLIN	01 02 04
0217	HUMAN EXPOS (PROD CONTAM)	01 02 04
0218	HUMAN EXPOS (ACCIDENTAL)	01 02 04
0219	HUMAN EXPOS (MONITORING)	01 02 04
0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
0240	METAB/PHARMACO (HUMAN)	01 02 04

INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

[redacted]

TRIAGE DATE: CAS SR

NON-CBI INVENTORY: (YES) NO IN TERMINI

ONGOING REVIEW: YES (DROP/REFER) NO (CONTINUE) REFER

SPECIES: RAT

TOXICOLOGICAL CONCERN: (LOW) MED HIGH

USE:

PRODUCTION:

COMMENTS: Rats were fed Terephthalic acid at dietary levels of 0, 1%, 2%, 5%. There was an increased mortality in the 5% TPA group. At lower dose levels no significant toxicity was observed.

CECATS\TRIAGE TRACKING DBASE ENTRY FORM

CECATS DATA:
Submission # 8EHQ- 0992 -13136 SEQ. A

TYPE (INT) SUPP FLWP

SUBMITTER NAME: E. I. Dupont de Nemours and Company

INFORMATION REQUESTED: FLWP DATE:
0501 NO INFO REQUESTED
0502 INFO REQUESTED (TECH)
0503 INFO REQUESTED (VOL ACTIONS)
0504 INFO REQUESTED (REPORTING RATIONALE)

DISPOSITION:
0659 REFER TO CHEMICAL SCREENING
0676 CAP NOTICE

VOLUNTARY ACTIONS:
0401 NO ACTION REPORTED
0402 STUDIES PLANNED/UNDERWAY
0403 NOTIFICATION OF WORKERS/USERS
0404 LABEL/MSDS CHANGES
0405 PROCESS/HANDLING CHANGES
0406 APP./U DISCONTINUED
0407 PRODUCTION DISCONTINUED
0408 CONFIDENTIAL

SUB. DATE: 09/11/92 OTS DATE: 09/22/92 CSRAD DATE: 03/23/95

CHEMICAL NAME: CAS# 100-21-0

INFORMATION TYPE:		P F C
0201	ONCO (HUMAN)	01 02 04
(0202)	ONCO (ANIMAL)	01 02 04
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0205	MUTA (IN VIVO)	01 02 04
0206	REPRO/TERATO (HUMAN)	01 02 04
0207	REPRO/TERATO (ANIMAL)	01 02 04
0208	NEURO (HUMAN)	01 02 04
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(0215)	CHRONIC TOX (ANIMAL)	01 (02) 04

INFORMATION TYPE:		P F C
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0220	ECO/AQUA TOX	01 02 04
0221	ENV. OCCC/REL/FATE	01 02 04
0222	EMER INCI OF ENV CONTAM	01 02 04
0223	RESPONSE REQEST DELAY	01 02 04
0224	PROD/COMP/CHEM ID	01 02 04
0225	REPORTING RATIONALE	01 02 04
0226	CONFIDENTIAL	01 02 04
0227	ALLERG (HUMAN)	01 02 04
0228	ALLERG (ANIMAL)	01 02 04
0239	METAB/PHARMACO (ANIMAL)	01 02 04
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INFORMATION TYPE:		P F C
0241	IMMUNO (ANIMAL)	01 02 04
0242	IMMUNO (HUMAN)	01 02 04
0243	CHEM/PHYS PROP	01 02 04
0244	CLASTO (IN VITRO)	01 02 04
0245	CLASTO (ANIMAL)	01 02 04
0246	CLASTO (HUMAN)	01 02 04
0247	DNA DAM/REPAIR	01 02 04
0248	PROD/USE/PROC	01 02 04
0251	MSDS	01 02 04
0299	OTHER	01 02 04

[redacted]

TRIAGE DATE: NON-CBI INVENTORY
(YES)
CAS SR NO
IN TRIAGE

ONGOING REVIEW
YES (DROP/REFER)
NO (CONTINUE)
REFER

SPECIES
RAT

TOXICOLOGICAL CONCERN:
LOW
(MED) CARCINOGENICITY
HIGH

USE:

PRODUCTION:

COMMENTS:

#13136A
M

Carcinogenicity is of medium concern based on the results of a 2-year feeding study in Wistar rats. Males and females (50/sex/dose) were fed concentrations of 1%, 2% and 5% (10000, 20000 and 50000 ppm, respectively). Tumors in the bladder/ureter developed in the high-dose groups (0/48, 2/47, 21/34 in males; 1/43, 1/48, 21/37 in females). Hyperplasia developed into papilloma and in some cases, squamous cell carcinoma and metaplasia occurred. Pituitary tumors were common in both sexes at all doses. Urinary tract stones and kidney nephropathy were reported primarily in the 5% group. Low incidence of tumors in the liver, lung, kidney and genital tract of both sexes were noted.